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Health and Environmental
Effects Profile for Diazinon

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HEALTH AND ENVIRONMENTAL EFFECTS PROFILE
FOR DIAZINON

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PREFACE

Health and Environmental Effects Profiles (HEEPs) are prepared for the Office of Solid Waste by the Office of Health and Environmental Assessment. The HEEP's are intended to support listings of hazardous constituents of a wide range of waste streams under Section 3001 of the Resource Conservation and Recovery Act (RCRA). Both published literature and information obtained from Agency program office files are evaluated as they pertain to potential human health, aquatic life and environmental effects of hazardous waste constituents. The literature searched and the dates of the searches are included in the section titled "Appendix: Literature Searched."

Quantitative estimates are presented provided sufficient data are available. For systemic toxicants, these include, Acceptable Daily Intakes (ADIs) for chronic exposures. An ADI is defined as the amount of a chemical to which humans can be exposed on a daily basis over an extended period of time (usually a lifetime) without suffering a deleterious effect. In the case of suspected carcinogens, ADIs are not estimated in this document series. Instead, a carcinogenic potency factor or q_1^* is provided. These potency estimates are derived for both oral and inhalation exposures where possible. In addition, unit risk estimates for air and drinking water are presented based on inhalation and oral data, respectively.

The first draft of this document was prepared by Syracuse Research Corporation under EPA Contract No. 68-03-3228. The document was subsequently revised after reviews by staff within the Office of Health and Environmental Assessment: Carcinogen Assessment Group, Reproductive Effects Assessment Group, Exposure Assessment Group, and the Environmental Criteria and Assessment Office in Cincinnati.

The HEEP's will become part of the EPA RCRA docket.

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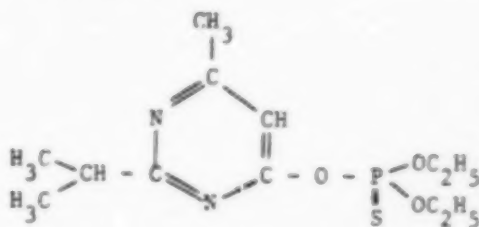
LIST OF ABBREVIATIONS

ADI	Acceptable daily intake
BCF	Bioconcentration factor
bw	Body weight
DNA	Deoxyribonucleic acid
EC ₅₀	Median effective concentration
LC ₅₀	Concentration lethal to 50% of recipients
LD ₅₀	Dose lethal to 50% of recipients
LOAEL	Lowest-observed-adverse-effect level
NOAEL	No-observed-adverse-effect level
NOEL	No-observed-effect level
ppm	Parts per million
SCE	Sister chromatid exchange
STEL	Short-term exposure limit
TLV	Threshold limit value
TWA	Time-weighted average
UDS	Unscheduled DNA synthesis

1. INTRODUCTION

1.1. STRUCTURE AND CAS NUMBER

Diazinon is the common name for 0,0-diethyl-0-(2-isopropyl-6-methylpyrimidin-4-yl) phosphorothioate or 0,0-diethyl 0-[6-methyl-2-(1-methylethyl)-4-pyrimidinyl]phosphorothioate (BCPC, 1977). It is also known by many other names; some of the more common ones include: phosphorothioic acid, 0,0-diethyl 0-[6-methyl-2-(1-methylethyl)-4-pyrimidinyl]ester; alfatox; basudin; diazide; diazitol; and phosphorothioic acid, 0,0-diethyl-0-(2-isopropyl-6-methyl-4-pyrimidinyl)ester (NIOSH, 1983). This insecticide was introduced in 1952 by T.R. Geigy S.A. under the code number "624480" and the trademarks "Basudin", "Diazitol", "Neocidol" and "Nucidol" (BCPC, 1977). The structure of diazinon is depicted below:



Molecular formula: $C_{12}H_{21}N_2O_3PS$

Molecular weight: 304.3

The Chemical Abstract Service (CAS) registry number for this compound is 333-41-5.

1.2. PHYSICAL AND CHEMICAL PROPERTIES

Pure diazinon is a colorless oil that is soluble in petroleum oils, and miscible with ethanol, acetone and xylene (BCPC, 1977). Diazinon decomposes above 120°C and is susceptible to oxidation; technical grade diazinon ($\geq 95\%$

pure) is a pale to dark brown liquid it is hydrolyzed by water and dilute acids (BCPC, 1977). Some of the physical properties of diazinon are listed below:

pK _a :	1.86 (Wolfe, 1980)
Boiling point:	83-84°C (BCPC, 1977)
Vapor pressure:	1.4 x 10 ⁻⁴ mm Hg at 20°C (BCPC, 1977)
Solubility:	40 mg/l at 20°C (BCPC, 1977)
Log organic matter partition coefficient:	2.12 (Briggs, 1981)
Log octanol/water partition coefficient:	3.11 (Briggs, 1981) 3.14 (Kanazawa, 1980)
BCF (experimental):	35 (Kenaga, 1980) 5.9-152 (Kanazawa, 1978)

1.3. PRODUCTION DATA

Diazinon is prepared by the condensation of O,O-diethyl phosphorochloridothioate with the pyrimidine prepared by the condensation of isobutyramine and ethyl 3-oxobutyrate (BCPC, 1977). Diazinon is produced by Consolidated Chemical Company in Palacios, Texas (U.S. EPA, 1983), Ciba-Geigy Corporation in McIntosh, Alabama, Velsicol Chemical Corporation in Chicago, Illinois (USITC, 1981) and Northwest Industries, Inc., in Bayport, Texas (SRI, 1983). The current U.S. production for this chemical was unavailable, but in 1977, Consolidated Chemical Co. produced 100,000-1,000,000 pounds (U.S. EPA, 1983). Since Consolidated Chemical Co. and Velsicol Chemical Corp. were not included in the 1983 Directory of Chemical Producers, it is unclear whether these companies are still producing diazinon.

1.4. USE DATA

Diazinon is a non-systemic insecticide with some acaricidal action. Its principal applications are on rice, fruit trees, vineyards, sugarcane, corn, tobacco, potatoes and horticultural crops. It is used to control a wide range of sucking and leaf-eating insects, and flies and ticks in veterinary practice (BCPC, 1977).

2. ENVIRONMENTAL FATE AND TRANSPORT PROCESSES

The fate of diazinon in soil and water environments has been well characterized. Experimental data suggest that chemical hydrolysis is an important mechanism in the degradation of diazinon. Getzin (1967) and Konrad et al. (1967) described the degradation of ^{14}C -diazinon in soil as involving hydrolysis at the heterocyclic phosphate bond followed by disruption of the cyclic moiety. The principal hydrolysis products formed were diethylthiophosphoric acid and 2-isopropyl-4-methyl-6-hydroxy-pyrimidine. Getzin (1968) further characterized the chemical hydrolysis of diazinon by measuring its disappearance in sterile and nonsterile soils with varying temperatures, pH and moisture content. The estimated half-lives were 5 weeks in the non-autoclaved soil and 6 weeks in the autoclaved soil. Increasing the temperature from 15 to 35°C resulted in an 8-fold increase in the disappearance rate in the non-sterile soil, and a reduction in moisture content from 30 to 2% increased the half-life to 16 weeks in the sterile soil. Diazinon has been found to be relatively stable at neutral pH and to disappear rapidly in acidic environments. The time for 50% loss in non-autoclaved soil at pH 4.3, 5.5, 6.7 and 8.1 were 1, 2, 4 and 6 weeks, respectively (Getzin, 1968).

The extent of diazinon degradation in soils may depend on the extent of initial adsorption of the compound to organic matter. Konrad et al. (1967) found rapid adsorption of diazinon in three soils followed by degradation at the adsorption sites. Greater adsorption was observed with increasing acidity and organic matter. Sharom et al. (1980a) observed rapid adsorption of diazinon in four soil types with maximum adsorption occurring in a soil with 75% organic matter. Briggs (1981) experimentally determined a log organic matter/water partition coefficient of 2.12 and a log octanol-water

partition coefficient of 3.11. Kenaga (1980) calculated a soil sorption coefficient of 530 for diazinon from binary regression equations. These data suggest that this compound may potentially sorb to organic matter in soils.

Microbial degradation may play a significant role in the disappearance of diazinon from soils. Early experimental data suggested that bacterial species such as Pseudomonas meolphtora (Boush and Matsumura, 1967) and an unidentified coccoidal rod (Gunner et al., 1966) were capable of degrading diazinon. Matsumura and Boush (1968) observed degradation of diazinon by the soil fungus, Trichoderma viride, and Gunner and Zuckerman (1968) reported a synergistic microbial action by Arthrobacter and Streptomyces on the degradation of diazinon. Several other investigators have attributed the disappearance of diazinon in soils to microbial actions. Miles et al. (1979) measured the half-life of diazinon in sterile and non-sterile organic and mineral soils (pH 6.8) and found it took an average of 10 weeks in the sterile soils and 1 week in the non-sterile soils for 50% of the compound to be degraded. During 1 month of incubation with bean plant roots, 12.9% of ^{14}C -diazinon was mineralized by associated rhizosphere microorganisms compared with 5.0% by the soil without roots (Hsu and Bartha, 1979). Microbial hydrolysis of diazinon has also been well demonstrated with extracts from mixed bacterial cultures (Akhyia et al., 1981; Munnecke, 1976). Diazinon had a half-life of <1 hour when incubated with Pseudomonas sp. cell extract (Barik and Munnecke, 1982), and 25 minutes with Flavobacterium sp. cell extract (Forrest et al., 1981; Brown, 1980).

The investigations on diazinon metabolism in flooded soils have been studied by Sethunathan and co-workers (Sethunathan, 1973, 1972; Sethunathan and Pathak, 1972; Sethunathan et al., 1971; Sethunathan and Yoshida, 1969;

Sethunathan and MacRae, 1969). Results of these studies can be summarized as follows: in neutral flooded soils, diazinon persisted for 2 months, whereas its persistence was considerably shorter in acidic soils if applied immediately after flooding. A biological degrading factor developed in flooded rice fields after repeated application of the insecticide, thus allowing an appropriate population of microorganisms to develop. 2-Iso-propyl-4-methyl-6-hydroxy-pyrimidine was recovered as the major metabolite in the anaerobic flooded soil. This product was resistant to further degradation under these anoxic conditions, suggesting that an oxygenase may be involved in the cleavage of the pyrimidine ring.

The two processes that may influence the transport of diazinon in the soil are leaching and volatilization. Both processes will depend on the degree of adsorption between the diazinon molecules and the soil complex and the water solubility of the compound. Sharom et al. (1980a) calculated "mobility factors" of 7.25 for sand and 3.13 for organic soil, which suggest that diazinon will leach more readily in soils low in organic matter. A "mobility factor" is proportional to the amount of compound leached by 10 successive 200 ml fractions through a soil column. Jenkins et al. (1978) measured the rate of volatilization of diazinon from five types of soils and found that volatilization was greatest from gravelly sand ($770 \text{ ng } 22 \text{ h}^{-1}$) and decreased as the organic matter content increased.

Chemical hydrolysis has been found to contribute to the disappearance of diazinon in the aquatic environment, with hydrolysis occurring more slowly at pH 5-9. This compound was found to be relatively stable in distilled water at pH 6.0, with a half-life of ~2-3 weeks (Coward et al., 1971); however, at 70°C in a buffer solution (pH 6.0) of ethanol and water (20:80), a half-life of 37 hours was reported by Ruzicka et al. (1967). At an

initial concentration of 6.61×10^{-3} M, half-lives of 0.5, 31, 185, 136 and 6 days were measured for diazinon at pH 3.1, 5.0, 7.4, 9.0 and 10.4, respectively, at 22°C in ethanol (Faust and Gomaa, 1972). This compound was rapidly degraded in acidic environments (pH 2) (Konrad et al., 1967; Getzin, 1967, 1968) and the rate of acid hydrolysis increased with increasing temperature (Meier et al. (1976).

Wolfe et al. (1976) determined a half-life of 1×10^{-3} hours for diazinon in an aqueous solution photolyzed in pyrex reaction cells using a medium-pressure mercury lamp (~280 nm), and Mitchell (1961) reported that diazinon was degraded by UV light; however, neither of these studies identified decomposition products. Pardue et al. (1970) identified hydroxydiazinon (0,0-diethyl-0-[2-(2'-propyl)-4-methyl-6-pyrimidinyl]phosphorothioate) by infrared, nuclear magnetic resonance, and mass spectrometry as a product of UV irradiation of diazinon.

Microbial degradation appeared to play an important role in the disappearance of diazinon from aqueous systems in the study of Sharom et al. (1980b). Diazinon disappeared more quickly from unsterilized natural water (12 weeks) than from unsterilized distilled or sterilized water (>16 weeks), suggesting that degradation is both biological and chemical in nature. Sethunathan and Yoshida (1969) and Sethunathan and MacRae (1969) reported that microorganisms played a significant role in the degradation of diazinon in flooded soils, but not in the degradation of its hydrolysis product (2-isopropyl-4-methyl-6-hydroxy-pyrimidine). It is likely, therefore, that in aqueous systems where diazinon does not undergo rapid chemical hydrolysis, microbial degradation may contribute significantly to its disappearance.

The transport of diazinon in aqueous systems will be influenced by its ability to volatilize from water, sorb to soil particles or bioaccumulate in

aquatic organisms. Although no specific data were located, volatilization does not appear to be a significant route of disappearance from aquatic systems.

Kanazawa (1978) determined values for BCF ranging from 5.9-152 for diazinon in various species of fish and snails, and Kenaga (1980) reported an experimental BCF of 35 for diazinon. These experimental values for BCF indicate that diazinon will not bioconcentrate to any great extent in aquatic organisms (Kenaga, 1980).

Data discussed previously suggest that diazinon may sorb to organic matter and be transported by this route in aquatic systems.

Pertinent data regarding the fate or transport of diazinon in the atmosphere were not located in the available literature. (See Appendix for literature searched; also additional classified data may be available. See Chapter 8 for a more complete explanation.)

3. EXPOSURE

STORET contained observations for 3730 stations for concentrations of diazinon in water. The overall analysis included: concentrations of diazinon in 21,978 whole water samples (0-33400.0 $\mu\text{g}/\text{L}$; mean of 1.7357); 3745 samples in mud (0-266.0 $\mu\text{g}/\text{kg}$; mean of 2.484 $\mu\text{g}/\text{kg}$); 359 samples of filtered water (0-0.999 $\mu\text{g}/\text{L}$; mean of 0.031 $\mu\text{g}/\text{L}$); and 201 samples of suspended water fraction (0-0.05; mean of 0.0018 $\mu\text{g}/\text{L}$).

Levels of 0-140.0 $\mu\text{g}/\text{L}$ (mean of 0.49 $\mu\text{g}/\text{L}$) were measured in Lake Erie sediment from 1975-1977 (Konasewich et al., 1978) and 0.07 $\mu\text{g}/\text{kg}$ in sediment in the Scioto River in Highby, Ohio (Ohio River Valley Water Sanit. Comm., 1978).

Johnson and Manske (1977) reported levels of 0.001-0.02 ppm diazinon in meats, vegetables, fruit and fat products from August, 1974 to July, 1975. Levels of 0.001-0.01 ppm diazinon were measured in foods contained in toddler and infant diets from August, 1975 to July, 1976 (Johnson et al., 1981).

An 8-hour TWA level of 100 $\mu\text{g}/\text{m}^3$ diazinon in work air was measured in a Houston pest control company, and a maximum of 41 $\mu\text{g}/\text{m}^3$ was detected around pest control operators (Hayes et al., 1980).

4. PHARMACOKINETICS

4.1. ABSORPTION

Dermal application of diazinon to calves (0.15-0.20% emulsions at 6-7 day intervals, total number of applications not reported) resulted in a 24-25% decrease in the activity of blood cholinesterase (Kan, 1971). This indicates that diazinon is absorbed following dermal application; however, the rate and extent of absorption were not measured.

Ahdaya et al. (1981) administered 1 μ Ci of 2-[^{14} C] diazinon (1 mg/kg) in Emulphor:ethanol:water (1:1:8) by gavage to fasted female ICR mice. Based on the radioactivity remaining in the gut contents at various times following administration, diazinon appeared to be absorbed rapidly from the gastrointestinal tract with a $t_{1/2}$ of 23.5 ± 2.1 minutes.

4.2. DISTRIBUTION

Maliwal and Guthrie (1981, 1983) found that human serum albumin contained 6-7 hydrophobic binding sites for diazinon. One was a high-affinity site and 4-6 were of moderate affinity. Changes in the absorption spectra indicated that tyrosyl and tryptophyl residues were located in the moderate-affinity sites. The presence of these binding sites would increase the solubility of diazinon in blood and facilitate the transport of diazinon throughout the body.

Muecke et al. (1970) administered 0.1 mg diazinon in water:ethanol (8:2) to male Wistar WU rats (~0.5 mg/kg) for 10 consecutive days. Animals were sacrificed at various times after the end of the dosing period and the radioactivity content of the major organs was determined. Originally, the highest levels of radioactivity were observed in the gastrointestinal tract, muscles, fat and liver. No significant radioactivity was detected in any tissue 2 days after the dosing period.

Ahdaya et al. (1981) investigated the distribution of diazinon in fasted female ICR mice following a single oral dose of 1 mg/kg. Diazinon was detected in the blood within 5 minutes of dosing, reached the maximum blood concentration in 15-20 minutes, and then remained at a constant level for at least an additional 40-45 minutes. Peak levels were reached in the liver earlier (~10 minutes); however, peak concentrations in the liver and blood were approximately equal.

Talanov (1978) injected (route unspecified) sheep with diazinon (20 g/kg). Five days after treatment, the residual levels were 0.4 mg/kg in fat and 0.01 mg/kg in muscle tissue. Avezov (1977) has suggested that beef cattle should not be slaughtered for at least 22 days following exposure, presumably because of residual tissue levels; however, the data to support this recommendation were not included in the abstract.

4.3. METABOLISM

Yang et al. (1969) have investigated the metabolism of diazinon by rat liver microsomes. The major route of diazinon metabolism involved oxidation via a carbon monoxide-sensitive enzyme system. The major products of this metabolism were diethyl phosphorothioic acid (DEPTA) and diethyl phosphoric acid (DEPA). Nakatsugawa et al. (1969) determined that the oxidative metabolism of diazinon involves two pathways, an oxidation to diazoxon followed by degradation to DEPA, or an oxidative degradation to DEPTA. These results have been confirmed by Dahm (1970) and Yang et al. (1971). Yang et al. (1971) also reported that nuclear, mitochondrial and soluble enzyme systems could catalyze the conversion of diazinon to DEPA; however, the microsomal enzymes were the most active.

In similar in vitro studies, Shishido et al. (1972a) found these same major metabolites and identified several other minor metabolites. They

reported that diazinon could be oxidized to diazoxon, hydroxydiazinon or hydroxydiazoxon. Oxidative cleavage of the aryl phosphate bond resulted in the formation of DEPA, DEPTA and 2-isopropyl-4-methyl-6-hydroxy-pyrimidine, 2-(2'-hydroxy-2'-propyl)-4-methyl-6-hydroxypyrimidine. DEPA was also formed by hydrolytic cleavage of the aryl phosphate bond of diazoxon; the reaction was catalyzed by a microsomal hydrolase that was not NADPH-dependent (Shishido and Fukami, 1972).

Shishido and Fukami (1972) compared the ability of a variety of rat tissue homogenates to hydrolyze diazinon. They found that the rates of metabolism decreased in the order: liver>blood>lung>heart>kidney>brain.

Shishido et al. (1972b) found that, in the rat, cleavage of the aryl phosphate bond of diazinon or diazoxon may also involve conjugation with glutathione, resulting in the production of S-(2-isopropyl-4-methyl-6-pyrimidinyl)-glutathione and DEPTA and DEPA, respectively. Liver tissue contained the greatest activity, but heart, brain, lung, kidney and blood tissues also catalyzed this reaction. Usui et al. (1977) investigated the activities of the various glutathione-S-transferases and found that cleavage of the aryl phosphate bond of diazinon was catalyzed by glutathione-S-transferases III and IV. Based on the comparison of in vitro enzyme activities of rat liver fractions with enzyme activities in the body fat of the cockroach, Shishido and Fukami (1972) concluded that the glutathione conjugation was less important in the rat than in the cockroach. Of the three metabolic processes (i.e., oxidation, hydrolysis and glutathione conjugation), the third is least important in the rat.

Sakai and Matsumura (1968, 1971) investigated the metabolism of diazinon by human and mouse brain esterases. These studies confirm that brain tissues contain enzyme systems for which organophosphate insecticides are substrates.

Machin et al. (1971, 1975) compared the metabolism of diazinon by hepatic microsomes and liver slices from sheep, cattle, pigs, guinea pigs, rats, turkeys, chickens and ducks. A number of metabolites were identified, including diazoxon, hydroxydiazinon, hydroxydiazoxon, isohydroxydiazinon, isohydroxydiazoxon, dehydrodiazinon and dehydrodiazoxon. The 6-aldehyde analogue of diazinon was tentatively identified, but firm structural identification was not obtained. Metabolic rates varied extensively between species; however, metabolic rates could not be correlated with toxicity.

The in vivo metabolism of diazinon has been investigated in rats (Muecke et al., 1970), sheep (Janes et al., 1973) and dogs (Iverson et al., 1975). Muecke et al. (1970) administered 1 mg diazinon in ethanol: water (2:8) by stomach tube or intravenously into the tail vein of male Wistar WU rats. The diazinon was labeled with ^{14}C in the pyrimidine ring. They found trace amounts of unmetabolized diazinon and three major metabolites, accounting for ~70% of the administered radioactivity, in the feces. These metabolites were identified as 1,6-dihydro-2-isopropyl-4-methylpyrimidine-6-one, 1,6-dihydro-2-(1-hydroxyisopropyl)-4-methylpyrimidine-6-one and 1,6-dihydro-2-(2-hydroxyisopropyl)-4-methylpyrimidine-6-one. The urine contained these three major metabolites and an undetermined number of more polar minor metabolites.

Janes et al. (1973) dosed two sheep with diazinon (1 g/kg) by stomach tube and collected urine for 2-3 days. Moderate, unspecified signs of poisoning were observed. One of the sheep was killed after 48 hours, the other was allowed to recover. Two metabolites were isolated from the urine and one was extracted from the fat of the slaughtered sheep. The two urinary metabolites were formed by hydroxylation of diazinon at the 2-isopropyl position (hydroxydiazinon) or at the methyl group. The metabolite found in the fat is formed by the dehydration of hydroxydiazinon.

Iverson et al. (1975) dosed two female beagle dogs with 4 mg diazinon/kg orally. Urine was collected over a 24-hour period and analyzed for metabolites. The metabolites isolated were identical to those found in rats by Muecke et al. (1970). These data indicate that rats and dogs, but not sheep, have efficient enzyme systems for cleavage of the aryl phosphate bond.

4.4. EXCRETION

Ahdaya et al. (1981) found that 26.4% of an oral dose of [2-¹⁴C] diazinon (1 mg/kg) administered to mice was excreted in the urine within 1 hour after dosing. Only trace amounts were detected as expired CO₂. Muecke et al. (1970) administered [2-¹⁴C] diazinon orally (0.8 mg/rat, ~4 mg/kg) to Wistar rats. Total recovery of radioactivity in the cage wash, urine, feces and expired air over a 168-hour period was 98.3% for males and 94.6% for females. In both sexes, the biological half-life was 12 hours and the expired air accounted for <0.05% of the administered radioactivity. In males, urinary excretion accounted for 80% of the dose and fecal excretion for 17.9%. In females, 68.9% was excreted in the urine and 25.4% in the feces. When male mice were dosed with [ethyl-¹⁴C] diazinon, the radioactivity displayed a biological half-life of 7 hours. Total recovery was 90.2%, with 5.6% excreted in the expired air, 65.4% in the urine and 18.9% in the feces.

The pharmacokinetic data indicate that diazinon is rapidly absorbed, metabolized and excreted. There was no indication that diazinon or its metabolites would accumulate in any tissue with increased time or repeated dosing.

5. EFFECTS

5.1. CARCINOGENICITY

The National Cancer Institute (NCI, 1979) has tested diazinon for carcinogenicity in F344 rats and B6C3F1 mice. Groups of 50 male or female rats were fed diets containing 400 or 800 ppm diazinon for 103 weeks. Females were sacrificed 1 week after the end of dosing and males after 2 weeks. Groups of 50 male or female mice were fed diets containing 100 or 200 ppm diazinon for 103 weeks and sacrificed after an additional 2 weeks. These levels had no appreciable effect on mortality or mean body weights of either sex of either species. It is probable that the high doses did not correspond to the maximally tolerated doses. No significant incidence of tumors occurred in the females of either species. In the low-dose groups, male rats had an excess of lymphomas or leukemias (25/50 compared with 5/25 in the controls, $p=0.011$) and male mice had an excess of hepatocellular carcinomas (20/46 compared with 4/21 in the controls, $p=0.046$). Tumor incidence in the high-dose groups, however, was not significantly greater than that of the controls. The authors concluded that the data did not support a correlation between diazinon administration and the development of tumors.

5.2. MUTAGENICITY

The mutagenicity of diazinon is summarized in Table 5-1. Diazinon has consistently produced negative results in all bacterial assays for mutagenicity either with or without metabolic activation by mammalian S9 mix.

Mixed results have been obtained in mammalian cell culture assays. In assays for SCE and UDS, only negative results have been obtained (Chen et al., 1981, 1982; Sobti et al., 1982; Waters et al., 1982). Positive results have been obtained when the endpoint used was chromosome breaks or chromosomal aberrations (Matsuoka et al., 1979; Tosoneva-Maneva et al., 1969, 1971).

TABLE 5-1
Mutagenicity of Diazinon

Assay	Indicator Organism	Application	Concentration or Dose	Activation System	Response	Reference
Reverse mutation	<i>S. typhimurium</i> TA1535, TA1537 TA1538, TA98 TA100	plate incorporation	up to 10 mg/plate	+/-	-	Waters et al., 1982
Reverse mutation	<i>S. typhimurium</i> TA98, TA100, TA1535, TA1537 TA1538	plate incorporation	NR	+/-	-	Moriya et al., 1983
forward mutation	<i>E. coli</i> K-12	plate incorporation	NR	-	-	Mohn, 1973a
forward mutation	<i>E. coli</i> NR	NR	NR	-	-	Mohn, 1973b
Reverse mutation	<i>E. coli</i> WP2uvrA	plate incorporation	up to 10 mg/plate	+/-	-	Waters et al., 1982
	<i>E. coli</i> WP2hcr	plate incorporation	NR	+/-	-	Moriya et al., 1983
Rec-assay	<i>B. subtilis</i> H17Rec ⁺ , M45Rec ⁻	spot test	NR	-	-	Shirasu et al., 1976
SCE	Chinese hamster V-79	liquid suspension	10-80 g/m.	+	-	Chen et al., 1982
SCE	Chinese hamster V-79	liquid suspension	10-40 g/m.	-	-	Chen et al., 1981
SCE	human lymphocyte	liquid suspension	0.02-2.0 g/m.	+	-	Sobti et al., 1982
Chromosomal aberrations	Chinese hamster lung	liquid suspension	0.1 mg/m.	+	+	Matsuoka et al., 1979
Chromosomal aberrations	human lymphocyte	liquid suspension	0.5 g/m.	-	+	Tosoneva-Maneva et al., 1969
Chromosome breaks	human lymphocyte	liquid suspension	NR	-	+	Tosoneva-Maneva et al., 1971
UDS	human lung fibroblast, WI-30	liquid suspension	NR	+/-	-	Waters et al., 1982

NR = Not reported

In a series of reports, Kiraly et al. (1976, 1977, 1979) described the results of chromosome studies in 34 workers involved in the production of diazinon in Budapest, Hungary. These workers had been involved in the production of pesticides for at least 6 months. The control groups consisted of 49 people presented for chromosome examination at the Genetic Counseling Center of the National Institute of Hygiene and who had no known exposure to mutagenic chemicals or radiation, and 14 factory employees who were never directly exposed to pesticides. The workshop air concentration was reported as 0.45 mg/m³, but exposure was limited by the use of "Tucan"-type face masks and air ventilation at least 15 times per hour. The exposed groups had an increased incidence of chromatid and chromosome aberrations compared with either control group.

Yoder et al. (1973) investigated the incidence of chromosomal aberrations in peripheral lymphocytes among 42 pesticide applicators in Idaho. The exposed group was divided into 16 workers exposed to insecticides, including diazinon, and 26 herbicide-exposed workers. The control population consisted of 16 businessmen, students, health professionals and teachers who had no history of pesticide exposure and who were matched with the exposed group as closely as possible as to ages and physical characteristics. Lymphocyte cultures were obtained during the peak spraying months and during mid-winter when pesticide exposure was minimal. A marked increase in the frequency of chromatid lesions, breaks and gaps occurred in the exposed population during the spraying season. The incidence of chromatid lesions was not significantly different from controls in the mid-winter samples.

5.3. TERATOGENICITY

Robens (1968, 1969) investigated the teratogenicity of diazinon in Golden Syrian hamsters (0.125 or 0.25 mg/kg) and New Zealand white rabbits (7 or 30 mg/kg). Oral administration of diazinon during organogenesis (days 6-8 in the hamster and 5-15 in the rabbit) did not produce any malformations in the fetuses examined. No increase in fetal mortality was observed.

Kimbrough and Gaines (1968) administered a single intraperitoneal dose of 100, 150 or 200 mg diazinon/kg bw to groups of six pregnant Sherman rats on day 11 of gestation. The fetuses were either fixed in Bouin's solution and examined by razor blade sectioning or fixed and stained with alizarin red for examination of bone structure. The highest dose resulted in an average of 11.0 resorptions per rat, compared with 0.8 resorptions per rat in the controls. Diazinon treatment resulted in the production of 1 hydrocephalus, 1 ectromelia and 1 missing first distal phalanx in the six surviving pups in the high-dose group.

Earl et al. (1973a,b) administered capsules containing diazinon corn oil at doses of 1, 2 or 5 mg/kg bw/day to groups of six beagle dogs or capsules containing 5 or 10 mg/kg bw/day to groups of seven Hormel-Hanford miniature swine throughout pregnancy. No malformations were observed in beagles at a dose of 1 mg/kg/day; however, at 2 mg/kg/day, nursing behavior was disturbed, resulting in the starvation of three pups in two different litters. Two cases of edematous thickened duodenal wall out of a total of 33 pups were observed at this dose level. At a dose of 5 mg/kg/day, one case of pronounced fontanelle with no teeth, one case of thickened duodenal wall, and one case of fibrous adhesions of the internal organs were observed out of a total of 49 pups. No abnormalities were observed in the offspring of the high-dose swine. In the low-dose groups, 3 of 48 swine were abnormal.

Two had malformations of the skull and one had malformed front limbs. No malformations were reported in the controls for either species.

Green (1970) fed Sprague-Dawley rats diets containing diazinon at the maximum allowable concentration for foodstuff for human consumption over four generations. This concentration was not specified. No malformations were observed; however, litter sizes were increased in all generations, and the fourth generation pups were smaller and matured much more slowly than the controls.

Barnett et al. (1980) and Cranmer et al. (1979) administered diazinon orally to F₂ dihybrid mice [(C57BL/6 x A/JAX) x (C34/He x BALB/C)] at doses of 0.18 or 9.00 mg/kg throughout gestation. No gross abnormalities were observed at birth; however, there was a high death rate due to respiratory infection that occurred between birth and weaning. Measurement of serum immunoglobulins indicated transient disturbances of IgG₁ and IgG_{2b}, which returned to normal by 400 days postpartum. These data suggest that diazinon may have an effect on the early development of the immune system. Diazinon treatment also perturbs adrenal function and inhibits hepatic metabolism of corticosterone (Cranmer et al., 1978).

A number of studies (Hoberman et al., 1979; Spyker and Avery, 1977) have investigated the effects of in utero exposure to diazinon on biochemical and behavioral functions. Hoberman et al. (1979) administered oral doses of diazinon in peanut oil (0, 40, 50, 60 or 75 mg/kg/day) to CFN rats on days 7-19 of gestation. The high dose was toxic to the dams. No gross abnormalities were observed in the remaining dose groups; however, brain esterase activity was reduced at all dose levels.

Spyker and Avery (1977) administered daily oral doses of 0, 0.18 or 9.00 mg diazinon/kg to groups of six pregnant mice throughout gestation. All

pups were grossly normal; however, the offspring from the high-dose group had reduced growth rates during the first month postpartum. Behavioral testing of the pups from the low-dose group revealed significantly ($p < 0.05$) delayed development of the contact placing reflex and of sexual maturity (i.e., descent of testes or vaginal opening). Delayed development was not observed in offspring from the high-dose group. On maturity, offspring from both treatment groups displayed impaired endurance and coordination. Microscopic examination revealed neuropathology (i.e., focal, dense aggregations of chromatin-containing cells) in the forebrains of mice from the high-dose groups at 101 days postpartum.

5.4. OTHER REPRODUCTIVE EFFECTS

Pertinent data regarding other reproductive effects of diazinon were not found in the available literature.

5.5. CHRONIC AND SUBCHRONIC TOXICITY

The National Cancer Institute (NCI, 1979) tested diazinon for carcinogenicity in F344 rats and B6C3F1 mice. The rats received diets containing 400 or 800 ppm (400 or 800 mg/kg diet) diazinon. The mice received diets containing 100 or 200 ppm (100 or 200 mg/kg diet). Fifty animals of each sex were exposed to each dose level for 103 weeks. Controls consisted of 25 animals per sex per species. Diazinon treatment did not adversely effect mean body weight, survival or the incidences of nonneoplastic lesions in either sex of either species. Some "hyperactivity" was noted in the dosed groups of both species. "Hyperactivity" was reported to be "rare" in the control groups of mice and was not mentioned for the control groups of rats. Other clinical signs reported for rats were discolored urine in the high-dose females and bloating and vaginal bleeding and discharge in dosed females. Tachypnea occurred at a higher incidence in treated groups of rats than in control groups of rats.

Earl et al. (1971) administered daily oral doses of 0, 2.5, 5.0, 10.0 or 20.0 mg diazinon/kg bw/day to groups of three male and three female beagle dogs and 0, 1.25, 2.5, 5.0 or 20.0 mg/kg bw/day to groups of three male and three female Hormel-Hanford swine for 8 months. Most of the animals in the high-dose groups died due to the toxicity of diazinon, but none of the animals died at the lower doses. There was a noticeable sex difference in susceptibility to diazinon toxicity, with male dogs being more sensitive than female dogs. In swine, this relationship was reversed and the differences were not as striking. Testicular atrophy was observed in two of the three high-dose male dogs before they died. The most common finding was edematous thickening of the small intestine in both species. Localized chronic nephritis was observed in two dogs receiving 10 mg/kg/day. Liver changes related to cirrhosis were observed in both species. The NOEL was 5 mg/kg/day in dogs. Some effects were seen at all dose levels in the swine.

In a series of studies, Davies and Holub (1979, 1980a,b) investigated the effects of dietary diazinon on male and female Wistar rats. In the initial studies, diets containing 0, 2 or 25 ppm diazinon were fed to groups of male and female rats for 7-30 days. Using acetylcholinesterase activity as the endpoint, females were found to be more sensitive than males, and plasma cholinesterase activity was found to be a more sensitive indicator of diazinon exposure than either brain or erythrocyte cholinesterase activity. Plasma cholinesterase activity was inhibited in females but not males at 2 ppm. At 25 ppm, plasma and erythrocyte cholinesterase activities were inhibited in both males and females, and brain cholinesterase activity was inhibited in females. In subsequent studies, groups of 50 female rats were fed diets containing 0, 5, 10 or 15 ppm diazinon for 92 days. Because maximal inhibition of cholinesterase activity was achieved in 35 days, after

which the extent of inhibition remained constant, the remaining experiments were conducted for shorter periods of time. Groups of 16 female rats were fed diets containing 1, 2, 3 or 4 ppm diazinon for 42 days and groups of 10 female rats were fed diets containing 0, 0.1, 0.5, 1.0 or 2.0 ppm diazinon for 35 days. Based on inhibition of plasma cholinesterase activity, a dietary level of 0.1 ppm, corresponding to a dose of 9 $\mu\text{g/kg bw/day}$, was the NOEL in these studies. Erythrocyte cholinesterase activity was reduced in groups receiving dietary levels ≥ 4 ppm diazinon. Brain cholinesterase activity was not inhibited at <15 ppm. No gross signs of toxicity such as tremors or hyperexcitability were noted at any of the dietary levels (0.1-25 ppm) employed in these studies. If inhibition of brain cholinesterase activity is considered to be a potential adverse effect, the results of the studies by Davies and Holub (1979, 1980a,b) suggest that levels of 1-15 ppm diazinon in the diet are NUAELs for the female rat. These dietary levels would correspond to dosages of 0.09-1.35 mg/kg bw/day , based on the ratio of dose to dietary level reported for 0.1 ppm. Similarly, 25 ppm, which may represent a LOAEL for the female rat, would correspond to 2.25 mg/kg bw/day .

Hinkle et al. (1980) exposed 80 Sprague-Dawley rats (40 males and 40 females) to atmospheres containing not more than 1.34 $\mu\text{g diazinon/m}^3$ (average = 0.82 $\mu\text{g/m}^3$) for 30 days. No changes in erythrocyte or plasma cholinesterase activity were detected as a result of this treatment.

5.6. OTHER RELEVANT INFORMATION

The acute toxicity of diazinon is summarized in Table 5-2. Diazinon is moderately toxic to mammals, with reported oral LD_{50} s ranging from 118-1200 mg/kg bw .

A number of interactive effects have been reported for diazinon. Keplinger and Deichmann (1967) investigated the interactive effects of

Table 5-2
Acute Toxicity of Diazinon

Species	Route of Exposure	LD ₅₀	Reference
Rat	oral	250 mg/kg	Gaines, 1969
Rat (male)	oral	300-850 mg/kg	Martin and Worthing, 1977
Rat (female)	oral	285 mg/kg	Gaines, 1969
Rat	dermal	500-1200 mg/kg	Noakes and Sanderson, 1969
Rat	dermal	>2150 mg/kg	Martin and Worthing, 1977
Rabbit	oral	118 mg/kg	Khaltov et al., 1973

simultaneous oral administration of several pesticide combinations in rats and mice. Administration of diazinon with aldrin or DDT resulted in a less than additive effect in the rat, implying some degree of antagonism between the effects of these chemicals. Synergistic effects were noted with aramite and diazinon in mice.

Dressel et al. (1979, 1982) demonstrated that acute pancreatitis may be induced in dogs by diazinon (75 mg/kg, administered intravenously) and secretion infusion (2 units/kg/hr). Pretreatment with atropine (200 µg/kg, administered intravenously), an inhibitor of cholinergic receptors, prevented the formation of these lesions.

A number of authors have indicated that much of the toxicity of diazinon preparations may be attributable to the presence of highly toxic impurities. Sulfotepp has been identified as a toxic impurity in many formulations of diazinon. Meier et al. (1979) demonstrated this compound to be relatively stable in the environment and to accumulate in areas where diazinon is used. Their analysis indicated that sulfotepp is introduced in the production process, is much more toxic to aquatic species than is diazinon, and may account for some of the insecticidal properties of diazinon formulations. Soliman et al. (1982) have indicated that improper storage of diazinon emulsifiable concentrate formulations can result in the conversion of diazinon into transformation products, including sulfotepp and monothiono-TEPP. Gaines (1969) has observed that the toxicity of diazinon to rats was directly proportional to the length of time the compound had been exposed to air.

Diazinon may also produce local effects when applied topically. Slem et al. (1972) investigated the effects of a number of pesticides on the rabbit eye. A 1% solution of diazinon resulted in corneal ulcer and purulent conjunctivitis within 30 days of treatment. No effects were observed with a 0.1% solution.

6. AQUATIC TOXICITY

6.1. ACUTE TOXICITY

The acute toxicity and lethal effects of diazinon were determined in many species of freshwater fish (Table 6-1). The most sensitive species tested was the cutthroat trout, Salmo clarkii, having a 96-hour LC_{50} value of 0.0017 mg diazinon/l (Johnson and Finley, 1980). Under similar test conditions, bluegill sunfish, Lepomis macrochirus, were more sensitive to diazinon than rainbow trout, Salmo gairdneri, having 96-hour LC_{50} values of 0.022 and 0.090 mg/l, respectively (Cope, 1965, 1966). The fathead minnow, Pimephales promelas, appears to be the most tolerant species tested, with 96-hour LC_{50} values of 3.7-10.3 mg diazinon/l (Dennis et al., 1979; Allison and Hermanutz, 1977; Meier et al., 1979). Carp (Cyprinus carpio), goldfish (Carassius auratus) and medaka (Oryzias latipes) may be similarly affected since their respective 48-hour LC_{50} values were 3.2, 5.1 and 5.3 mg diazinon/l (Hashimoto and Nishiuchi, 1981).

The marine sheepshead minnow, Cyprinodon variegatus, had a 96-hour LC_{50} value, determined in a flowthrough system, of 1.470 mg diazinon/l (Goodman et al., 1979).

Histopathological changes in the liver, digestive system, kidney and gills have been reported in two species of fish treated with diazinon (Sastry and Sharma, 1981; Sastry and Malik, 1982). Following 15 and 30 days of exposure to 0.2 and 0.4 mg diazinon/l, the liver of Ophiocephalus punctatus became severely damaged with fibrosis, degenerative hepatocyte nuclei and necrosis, especially in the centrilobular area (Sastry and Sharma, 1981). Changes of the stomach and the intestine of O. punctatus were slight and included some cellular erosion of the mucosa and degenerative villi. Renal damage increased in severity with time to include

TABLE 6-1

Acute Lethal Effects of Diazinon to Freshwater Fish

Species	Duration (hours)	Concentration (mg/L)	Method	Effect	Reference
Rainbow trout, <u>Salmo gairdneri</u>	96	0.12	static	LC ₅₀	Meier et al., 1976
Rainbow trout, <u>S. gairdneri</u>	96	0.090	static	LC ₅₀	Johnson and Finley, 1980
Rainbow trout, <u>S. gairdneri</u>	3	5.0	static	100% mortality	Applegate et al., 1957
Rainbow trout, <u>S. gairdneri</u>	24 48 96	0.380 0.170 0.090	static static static	LC ₅₀ LC ₅₀ LC ₅₀	Cope, 1965 Cope, 1965, 1966 Cope, 1965
Rainbow trout, <u>S. gairdneri</u>	96	1.35	static	LC ₅₀	Meier et al., 1979
Cutthroat trout, <u>Salmo clarkii</u>	96	0.0017	static	LC ₅₀	Johnson and Finley, 1980
Lake trout, <u>Salvelinus namaycush</u>	96	0.602	static	LC ₅₀	Johnson and Finley, 1980
Brook trout, <u>Salvelinus fontinalis</u>	96	0.770	flowthrough	LC ₅₀	Allison and Hermanutz, 1977
Bluegill sunfish, <u>Lepomis macrochirus</u>	96	0.13	static	LC ₅₀	Meier et al., 1976
Bluegill sunfish, <u>L. macrochirus</u>	96	0.168	static	LC ₅₀	Johnson and Finley, 1980
Bluegill sunfish, <u>L. macrochirus</u>	2	5.0	static	100% mortality	Applegate et al., 1957
Bluegill sunfish, <u>L. macrochirus</u>	24 48 96	0.052 0.030 0.022	static static static	LC ₅₀ LC ₅₀ LC ₅₀	Cope, 1965 Cope, 1965, 1966 Cope, 1966
Bluegill sunfish, <u>L. macrochirus</u>	48	0.086	static	LC ₅₀	Cope, 1966
Bluegill sunfish, <u>L. macrochirus</u>	48	0.030	static	LC ₅₀	FMPCA, 1968
Bluegill sunfish, <u>L. macrochirus</u>	96	0.460	flowthrough	LC ₅₀	Allison and Hermanutz, 1977
Bluegill sunfish, <u>L. macrochirus</u>	96	0.53	static	LC ₅₀	Dennis et al., 1979
Bluegill sunfish, <u>L. macrochirus</u>	96	0.12	static	LC ₅₀	Meier et al., 1979
Carp, <u>Cyprinus carpio</u>	48	3.2	NR	LC ₅₀	Hashimoto and Mishiuchi, 1981
Goldfish, <u>Carassius auratus</u>	48	5.1	NR	LC ₅₀	Hashimoto and Mishiuchi, 1981

TABLE 6-1 (cont.)

Species	Duration (hours)	Concentration (mg/L)	Method	Effect	Reference
Fathead minnow, <u>Pimephales promelas</u>	96	7.800	flowthrough	LC50	Allison and Hermantutz, 1977
Fathead minnow, <u>P. promelas</u>	96	3.7	static	LC50	Dennis et al., 1979
Fathead minnow, <u>P. promelas</u>	96	10.3	static	LC50	Meier et al., 1979
Fathead minnow, <u>P. promelas</u>	96	6.9	flowthrough	LC50	Jarvinen and Tanner, 1982
Pond loach, <u>Misgurnus anguillicandatus</u>	48	0.5	NR	LC50	Hashimoto and Mishiuchi, 1981
Harlequin fish, <u>Rasbora heteromorpha</u>	24	1.45	static	LC50	Alabaster, 1969
Flagfish, <u>Jordanella floridae</u>	96	1.600	flowthrough	LC50	Allison and Hermantutz, 1977
Singhi, <u>Saccrobranchus fossilis</u>	24	3.03	static	LC50	Verma et al., 1982
	48	2.75	static	LC50	Verma et al., 1982
	72	2.39	static	LC50	Verma et al., 1982
	96	2.27	static	LC50	Verma et al., 1982
Medaka, <u>Oryzias latipes</u>	48	5.3	NR	LC50	Hashimoto and Mishiuchi, 1981
<u>Tilapia mossambica</u>	96	625 mg/kg ^a	static	LC50	Qadri et al., 1982
	96	50 mg/kg ^b	static	LC50	
Lamprey larvae, <u>Petromyzon marinus</u>	12	5.0	static	100% mortality	Applegate et al., 1957

^aTechnical (90%) diazinon was administered in the diet.

^bA diazinon formulation (EC20 formulation) was administered in the diet.

NR = Not reported

proximal tubule damage, glomerular shrinkage, desquamation of tubules and ruptured distal tubules. Heteropneustes fossilis exposed to 3.3 mg diazinon/l for 15 and 30 days had similar damage to the liver, stomach and intestine (Sastry and Malik, 1982). Centrilobular damage was more extensive, with vacuolated hepatocytes and enlarged nuclei. Slight erosion of the stomach mucosa was reported. Columnar epithelium of the intestine, however, was more severely affected, having necrosed villi and degenerative apical cell membranes and cytoplasm.

The acute toxicity of diazinon has been determined for several daphnids, scuds and stonefly larvae (Table 6-2). Daphnids are consistently more sensitive to diazinon than other species tested, including the fish. Diazinon at a concentration as low as 0.0008 mg/l caused loss of equilibrium in Daphnia pulex in 48-hour bioassays (Johnson and Finley, 1980). Daphnia magna and Simocephalus serrulatus appeared to be similarly affected by diazinon, with 48-hour LC_{50} values near 0.002 mg/l (Sanders and Cope, 1966; Meier et al., 1976, 1979). The scud, Gammarus lacustris, was more resistant to diazinon, with 24-, 48- and 96-hour LC_{50} values of 0.80, 0.50 and 0.20 mg/l, respectively (Sanders, 1969).

6.2. CHRONIC EFFECTS

The effects of diazinon exposure on embryo development and survival of carp, Cyprinus carpio, were determined by Malone and Blaylock (1970). At 1.0 mg diazinon/l, 100% mortality was noted during three replicate tests, while mortality of embryos exposed at 0.1 mg diazinon were not significantly ($p < 0.05$) different from controls (2.6% mortality).

During 32-day embryo-larval studies in fathead minnows, diazinon at ≥ 0.090 mg/l concentrations significantly ($p < 0.05$) reduced the mean weight

TABLE 6-2
Acute Lethal Effects of Diazinon to Other Aquatic Species

Species	Duration (hours)	Concentration (mg/L)	Method	Effect	Reference
Water flea, <u>Daphnia magna</u>	48	0.0023	static	EC ₅₀ *	Meier et al., 1976
Water flea, <u>Daphnia magna</u>	48	0.00125	static	LC ₅₀	Dennis et al., 1979
Water flea, <u>Daphnia magna</u>	48	0.0020	static	EC ₅₀	Meier et al., 1979
Water flea, <u>Daphnia magna</u>	48	0.0008	static	EC ₅₀	Johnson and Finley, 1980
Water flea, <u>Daphnia pulex</u>	48	0.0009	static	LC ₅₀	FMPCA, 1968
Water flea, <u>Daphnia pulex</u>	48	0.0009	static; 50°F	EC ₅₀	Sanders and Cope, 1966
Daphnid, <u>Simocephalus serrulatus</u>	48	0.0014	static	EC ₅₀	Johnson and Finley, 1980
Daphnid, <u>S. serrulatus</u>	48	0.002	static	EC ₅₀	Cope, 1966
Daphnid, <u>S. serrulatus</u>	48	0.0018 0.0014	static; 60°F static; 70°F	EC ₅₀ EC ₅₀	Sanders and Cope, 1966
Scud, <u>Gammarus fasciatus</u>	48	0.0002	static	EC ₅₀	Johnson and Finley, 1980
Scud, <u>Gammarus lacustris</u>	48	0.500	static	LC ₅₀	FMPCA, 1968
Scud, <u>Gammarus lacustris</u>	24 48 96	0.80 0.50 0.20	static static static	LC ₅₀ LC ₅₀ LC ₅₀	Sanders, 1969 Sanders, 1969 Sanders, 1969
Stonefly, <u>Pteronarcys callifornica</u>	48	0.025	static	EC ₅₀	Johnson and Finley, 1980
Stonefly, <u>P. callifornica</u>	48	0.060	static	LC ₅₀	FMPCA, 1968
Juvenile mysid shrimp, <u>Mysidopsis bahia</u>	96	0.005	flowthrough	LC ₅₀	Mimmo et al., 1981

*EC₅₀ = Concentration for loss of equilibrium or death in 50% of the test animals.

gain of exposed fish (Jarvinen and Tanner, 1982). Mortality was significantly ($p < 0.05$) increased in larvae exposed at 0.290 and 0.500 mg diazinon/l, but embryo hatching was not adversely affected at these concentrations. No effects of diazinon were reported in any fish exposed at 0.050 mg diazinon/l (Jarvinen and Tanner, 1982).

The effects of diazinon on egg hatching and embryologic development in carp, Cyprinus carpio communis, were examined by Kaur and Toor (1977). In controls, hatching success was 95%. Hatching success among eggs exposed to diazinon at 0.01, 0.05, 0.1, 1.0 and 1.5 mg/l were 43.7, 30.7, 28.5, 12.0 and 8.3%, respectively. Deformities, including caudal undevelopment and vertebral malformations, were high in low dose groups (38.4 and 25% for 0.01 and 0.05 mg diazinon/l, respectively) and too few embryos survived in high dose groups to interpret data. Based on these studies, the authors (Kaur and Toor, 1977) reported an EC_{50} for egg hatching to be 0.008 mg diazinon/l.

Goodman et al. (1979) exposed sheephead minnows, Cyprinodon variegatus, to diazinon in partial life-cycle tests to determine the chronic toxic and embryo-larval effects. During exposure, juvenile minnows were allowed to mature and reproduce, and effects on egg production, egg fertility, embryo survival and embryo development were determined. Groups were exposed at 0.00047, 0.00098, 0.0018, 0.0035, 0.0065 mg diazinon/l for a total of 108 days with a 32-day recovery period. No diazinon-related mortality among parental C. variegatus was reported, but signs of stress among fish of the three highest dose groups were cited as signs of toxicity (Goodman et al., 1979). Egg production in exposed minnows was significantly reduced ($p < 0.05$) in a dose-related fashion in all exposed groups. Fertility of eggs, however, was not affected. Mortality and development of embryos and juvenile

progeny were not affected by parental or embryonic (during 28 days post-fertilization) exposure to diazinon at the concentrations tested (Goodman et al., 1979). Based on the significant decrease in egg production, the maximum acceptable toxicant concentration for diazinon in sheepshead minnows was <0.00047 mg/l.

Estuarine mysid shrimp, Mysidopsis bahia, were exposed to diazinon at various concentrations for 28 days (through two life cycles) (Nimmo et al., 1981). The maximum acceptable toxicant concentration was determined to be between 0.00115 and 0.00327 mg diazinon/l for continued survival and reproduction. The most sensitive factor during the chronic exposure was not reproductive success or survival of juvenile stages, but survival of the adults throughout the life cycle (Kinno et al., 1981).

6.3. PLANT EFFECTS

The blue-green algae, Cylindrospermum sp., tolerated levels of diazinon as high as 300 mg/l for 7 and 18 days of exposure before growth was dramatically reduced (Singh, 1973). Two other species of blue-green algae, Aulosira fertilissima and Plectonema boryanum, were not affected at levels up to 600 mg diazinon/l.

Diazinon at nominal concentrations of 0.1 and 1.0 mg/l for 10 days had no effect on cell number, biomass or uptake of carbon-14 as a measure of photosynthesis in the green alga, Scenedesmus quadricaudata (Stadnyk et al., 1971).

6.4. RESIDUES

The BCF of diazinon in sheepshead minnows, Cyprinodon variegatus, was determined to be 147 for fish exposed to 0.0018 and 0.0035 mg/l and 213 for fish exposed to 0.0065 mg/l (Goodman et al., 1979). Uptake was rapid and reached a steady state within 4 days of exposure. Seguchi and Asaka

(1981) reported BCFs of 130, 92, 24 and 4 for carp, rainbow trout, loach and shrimp, Penaeopsis joyneri, respectively. Steady-state BCFs were reached by 3 days of exposure in this study (Seguchi and Asaka, 1981). The BCF for diazinon in Pseudorasbora parva (commonly motsugo) was 64 after 30 days of exposure (Kanagawa, 1975) and was also reported as 152 for the same species (Kanazawa, 1982). Miller et al. (1966) reported that killifish, Fundulus heteroclitus, and mussels, Elliptio complanatus, accumulated diazinon rapidly in concentrated water, but rapidly excreted diazinon as water levels decreased.

Diazinon was detected in all whole-water samples analyzed by Miles (1976) and Miles and Harris (1978) from streams in Ontario, Canada. Diazinon appears to remain in solution and does not adsorb onto sediments (Miles, 1976). Its degradation is ~75% within 30 days (Kanazawa, 1975). Carp, whitefish and minnows were found to contain 0.07, 0.01 and <0.01 mg/kg diazinon, while other fish species contain undetectable levels (Miles and Harris, 1978).

6.5. OTHER RELEVANT INFORMATION

Microsomal preparations of the liver of channel catfish, Ictalurus punctatus, metabolized diazinon, in vitro, to diazoxon and other water-soluble metabolites (Hogan and Knowles, 1972). More recently, Fujii and Asaka (1982) reported that liver preparations from carp, rainbow trout, channel catfish, dace (Tribolodon hakonensis) and yellow tail (Seriola quinqueradiata) metabolized diazinon, hydroxy methyl diazinon, hydroxy pyrimidine and diazoxon. Changes in hepatocytes have been reported within 24 hours of diazinon treatment (0.37 mg/l) in Channa punctatus (Anees, 1978). Intestinal damage, including degenerative muscular layers and necrosis of the submucosal area, was noted after 96 hours and 14 days of exposure to diazinon at 0.28 and 0.15 mg/l, respectively (Anees, 1976).

Diazinon exposure has been shown to significantly ($p < 0.05$) inhibit brain acetylcholinesterase activity soon after exposure in sheepshead minnows treated at 0.00047 mg/l (Goodman et al., 1979). Sporadic significant decreases in brain acetylcholinesterase activity were reported within 4 days in fish treated at 0.00047 and 0.00098 mg diazinon/l while those treated at 0.0018 and 0.0035 mg/l showed consistently depressed brain acetylcholinesterase activity from day 4 throughout the 108-day study. Treatment at 0.0065 mg diazinon/l depressed brain acetylcholinesterase activity levels by 63% within 1 day of exposure and continued to be significantly ($p < 0.05$) reduced throughout the study (Goodman et al., 1979). Diazinon treatment (0.31 mg/l) has caused a reduction in the activity of brain alkaline phosphatase, acid phosphatase, glucose 6-phosphatase, lactic dehydrogenase, pyruvic dehydrogenase and succinic dehydrogenase in addition to depressed acetylcholinesterase activity (Sastry and Sharma, 1980). Sodium-potassium activated adenosine triphosphatase activity was slightly elevated after 96 hours and 15 days of exposure.

7. EXISTING GUIDELINES AND STANDARDS

7.1. HUMAN

The American Conference of Governmental Industrial Hygienists (ACGIH, 1980, 1982) have established a TLV of 0.1 mg/m³ and a STEL of 0.3 mg/m³. According to the Code of Federal Regulations (1982), the U.S. EPA has established tolerances for food crops ranging from 0.05-1.0 ppm.

The WHO/FAO (World Health Organization/Food and Agriculture Organization) has recommended an ADI of 2 µg/kg bw/day based on NOELs for plasma cholinesterase inhibition in dogs and humans and a safety factor of 10 (Vettorazzi, 1975). These NOELs were derived from unpublished studies. The human study, performed by Industrial Bio-Test Labs, was subsequently found to be invalid (U.S. EPA, 1982).

The U.S. EPA (Office of Pesticide Programs) derived an ADI for diazinon, after considering a 106-week feeding study in monkeys, a 90-day feeding study in rats, a 90-day feeding study in dogs, a 2-year feeding study in rats, a 2-year feeding study in dogs, a teratology study in rabbits and a demyelination study in hens that are not available in the open literature (Federal Register, 1981, 1982). No details of these studies were provided in the Federal Register. Based on cholinesterase inhibition in the 90-day feeding study in dogs, a NOEL of 20 µg/kg bw/day was identified. Using this NOEL and an uncertainty factor of 10, the U.S. EPA derived an ADI of 2 µg/kg bw/day.

7.2. AQUATIC

Guidelines and standards for the protection of aquatic organisms from the toxic effects of diazinon were not located in the available literature.

8. RISK ASSESSMENT

The carcinogenicity of diazinon has been investigated in a 103-week feeding study using F344 rats and B6C3F₁ mice (NCI, 1979). Groups of 50 animals of each sex were given diets containing 400 or 800 ppm (400 or 800 mg/kg diet) diazinon (rats) or 100 or 200 ppm (100 or 200 mg/kg diet) diazinon (mice). Assuming that a rat consumes a daily amount of food equal to 5% of its body weight, and that a mouse consumes a daily amount of food equal to 13% of its body weight, these dietary levels would correspond to 20 or 40 mg diazinon/kg bw/day for the rats and 13 and 26 mg/kg bw/day for the mice. There was no correlation between diazinon administration and the development of tumors. No treatment-related non-neoplastic lesions were observed in either species, but some overt signs of toxicity were observed in dosed groups of both species. These signs of toxicity included hypersensitivity in dosed male and female mice and rats, tachypnea in dosed male and female rats, bloating and vaginal bleeding and discharge in dosed female rats, and discolored urine in high-dose female rats. Actual incidences were not reported, so the significance of these findings is unclear.

Earl et al. (1973a,b) administered capsules containing 0, 1, 2 or 5 mg diazinon/kg bw/day to groups of six pregnant beagle dogs throughout gestation. No statistical analyses were performed, but malformations were observed only in groups that received 2 or 5 mg/kg bw/day. This study has been reviewed by the EPA and was considered to be inadequate in terms of numbers of animals used and observation of the dams during treatment (Federal Register, 1980).

Several publications from a single laboratory have reported numerous biochemical effects of in utero exposure to doses of diazinon as low as 0.18 mg/kg bw/day throughout gestation (Barnett et al., 1980; Cranmer et al., 1978, 1979; Hoberman et al., 1979; Spyker and Avery, 1977). Histological

examination revealed neuropathology at 10 days postpartum in the forebrains of mice exposed in utero to 9 mg/kg bw/day throughout gestation (Spyker and Avery, 1977). Behavioral defects (delayed development and impaired endurance and coordination) were observed at the lowest dose used (0.18 mg/kg bw/day) (Spyker and Avery, 1977).

Significant differences in species susceptibility to diazinon toxicity have been reported by Earl et al. (1971). No histological changes were noted in six beagle dogs that received daily oral dose of 5 mg/kg bw/day for 8 months, but signs of toxicity (hemorrhage of the intestinal tract and slight cirrhotic changes in the liver) were observed in miniature swine at the lowest dose tested (1.25 mg/kg bw/day for 8 months).

Other investigators have used inhibition of plasma cholinesterase, rather than actual adverse effects, as the endpoint of their studies. In a series of experiments, Davies and Holub (1979, 1980a,b) fed diets containing 0.1-25 ppm diazinon to rats for 35-92 days. The 0.1 ppm level (9 µg/kg bw/day) was a NOEL for inhibition of serum, erythrocyte and brain cholinesterase activity. Dietary levels of 1-15 ppm (0.09-1.25 mg/kg bw/day) were NOAELs; serum and erythrocyte cholinesterase inhibition occurred, but brain cholinesterase activity was not inhibited and no overt signs of toxicity were observed. At 25 ppm (2.25 mg/kg bw/day), brain cholinesterase was inhibited but no outward signs of toxicity were seen.

While 9 µg/kg bw/day appears to be a reasonable approximation of the threshold for serum cholinesterase inhibition, the threshold for adverse effects is much higher. The lowest dose at which adverse effects have been reported is 0.18 mg/kg bw/day in a behavioral teratology study in mice (Spyker and Avery, 1977). Slightly higher doses (1.25 mg/kg bw/day) have produced histopathological effects in an 8-month oral dosing study in miniature pigs (Earl et al., 1971). No clearly adverse effects have been

reported at doses less than the LOAEL of 0.18 mg/kg bw/day. The highest reported suitable NOAEL that is not higher than or equal to this LOAEL would therefore be the dietary level of 1 ppm diazinon (~0.09 mg/kg bw/day) from the subchronic dietary studies of Davies and Holub (1979, 1980a,b). This dosage level inhibited serum and erythrocyte cholinesterase but not brain cholinesterase activity in female rats and produced no overt signs of toxicity, such as tremors or hyperexcitability. Because the results of chronic feeding studies (NCI, 1979) have indicated that mice can tolerate 26 mg/kg bw/day and rats can tolerate 40 mg/kg bw/day of diazinon with no histopathologic effects or adverse effects on survival (although some hyperactivity was noted), an uncertainty factor of 100 (10 to account for interspecies extrapolation and 10 for protection of unusually sensitive individual within the population) may be appropriate. Application of this uncertainty factor results in an ADI of 0.9 μ g/kg bw/day or 63 μ g/day for a 70 kg man.

Statements concerning available literature in this document refer to published, quotable sources and are in no way meant to imply that confidential data, which this document could not address, are not in existence. These data, which are considered Confidential Business Information (CBI), are available in summary form as a CBI Appendix that can be accessed by individuals with appropriate clearance. Conclusions from the CBI Appendix regarding risk assessment can be presented in this chapter.

The additional animal data reviewed in the CBI Appendix do not necessitate a change in the ADI derived above. Although chronic oral NOAELs of ~0.5 mg/kg bw/day were determined for rats and monkeys, these values could not be used as the basis for an ADI because they are higher than the LOAEL of 0.18 mg/kg bw/day previously described. These CBI data do, however, provide additional support for the uncertainty factor of 100 used above in estimating the ADI from a subchronic animal NOAEL.

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APPENDIX: LITERATURE SEARCHED

This profile is based on data identified by computerized literature searches of:

CA SEARCH (Files 308, 309, 310, 311, 320)
TOXLINE
MEDLINE
RTECS
SCI SEARCH
OHM TADS
STORET
SRC Environmental Fate Data Bases
SANSS
AQUIRE

These searches were conducted in July and August 1983. In addition, hand searches were made of Chemical Abstracts (Collective Indices C and 7th), and the following secondary sources were reviewed:

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